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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,080	10/28/1999	FRANK J. GONZALEZ	15280-271100	5674

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No. 09/308,080	Applicant(s) GONZALEZ ET AL.	
	Examiner Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Notice of References Cited	Application/Control No. 09/308,080	Applicant(s)/Patent Under Reexamination GONZALEZ ET AL.	
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U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
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	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 95/28489	10-1995	WIPO		
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Bork , Genome Research, 10:398-400, 2000
	V	Broun et al. , Science 282:1315-1317, 1998.
	W	Van de Loo et al. , Proc. Natl. Acad. Sci. 92:6743-6747, 1995.
	X	Seffernick et al. , J. Bacteriol. 183(8):2405-2410, 2001.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 09/308,080	Applicant(s)/Patent Under Reexamination GONZALEZ ET AL.	
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	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Witkowski et al. , Biochemistry 38:11643-11650, 1999
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

DETAILED ACTION

Status of the Application

Claims 1-11 are pending.

It is noted that examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/2003 has been entered.

Applicant's cancellation of claims 15-17, 20-28, and amendment of claims 1, 3-4, 6, 8-11 in Paper No. 22, filed on 12/10/2002 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/013,835 filed on 03/20/1996.

2. This application is the national stage of PCT/US97/04269, filed on 03/19/1997

Drawings.

3. The drawings have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Objections

4. Claims 3, 8 and 11 are objected to because of the recitation of "primer from about 15 to about 20 nucleotides long and wherein the nucleotides are in a sequence complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861 (534)". For clarity, it is suggested that the claims be amended to recite "primer from about 15 to about 20 nucleotides long and wherein said primer is ....complementary to the polynucleotide of SEQ ID NO: 1 between positions 434 and 861 (534)" or similar. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 3, 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 3, 8, 10 and 11 are indefinite in the recitation of "wherein the nucleotides are in a sequence complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861 (534)" for the following reasons. As written, the term "complementary" is indefinite since it is unclear if the probes are completely complementary or partially complementary to the fragments

of the polynucleotide of SEQ ID NO: 1 recited. For example, the probe may have a few nucleotides which are not identical to the corresponding fragment of the polynucleotide of SEQ ID NO: 1. It is suggested that if the intended probes are completely complementary to the corresponding fragments of the polynucleotide of SEQ ID NO: 1, the claims be amended to recite "wherein the probe is completely complementary to the polynucleotide of SEQ ID NO: 1 between positions 434 and 861 (534)" or similar. For examination purposes, it will be assumed that the intended probes are completely complementary to the recited fragments. Correction is required.

8. Claim 6 (claims 7-9 dependent thereon) is incomplete as it appears an additional step is required in order to determine whether the presence of A or G at position 434 is indicative of sensitivity to 5-FU. As written, it is not clear from the claim as to which nucleotide at position 434 of SEQ ID NO:1 indicates sensitivity to 5-FU. The specification discloses that "patients in whom 5-FU is severely toxic typically have low levels of dihydropyrimidine dehydrogenase (DPD) activity" (page 1, lines 25-26) and Example II (pages 23-28 of the instant specification) provides evidence that reduced DPD activity resulting from the splicing defect causes 5-FU toxicity. It is suggested that, for example, applicant identify which nucleotide (A or G) at position 434 results in 5-FU sensitivity. Correction is required.

9. Claim 10 (claim 11 dependent thereon) is indefinite in the recitation of "wherein the nucleotide sequence" since there is no antecedent basis for the nucleotide sequence. For examination purposes, the claim will be interpreted as being drawn to a composition comprising a polymerase chain reaction primer from about 15 to about 20 nucleotides long, wherein the

primer is complementary to the polynucleotide of SEQ ID NO: 1 between positions 434 and 861. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

12. This rejection has been discussed at length in previous Office Action Paper No. 10, mailed on 4/18/2001.

13. In regard to the genus of dihiydropyrimidine dehydrogenase (DPD) genes, Applicants argue that the claims have been amended to recite the sequence of the splice junction comprising the site of mutation at position 434 of SEQ ID NO:1. Furthermore, Applicants argue that the claims are not drawn to a genus of DPD genes and are instead drawn to methods operating upon the genus. Applicants submit that the method has been applied to a heterogeneous population of subjects. Applicant argues that even a single species of a recited genus can be sufficient to claim a genus as a whole. Applicant argues that, in accordance with *In re Herschler* (591 F.2d 693,

697, 200 USPQ 711, 714 (CCPA 1979)), the functional description of the claimed methods would lead one of ordinary skill to test the compounds on the genus of DPD genomic DNAs.

14. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. In regard to arguments that the method has been applied to a heterogeneous population of subjects, it is noted that the written description rejection has been applied in view of the fact that the genus of DPD genes required to practice the method has not been adequately described, and not because one cannot practice the claimed method with people of different ethnic backgrounds. It is not the Examiner's contention that the claimed method cannot be practiced with other human DPD genes but rather whether the skilled artisan would recognize that applicants were in possession of the invention at the time of filing in view of the fact that only one species of the genus of genes is described. While it is acknowledged that the claims are not drawn to DPD genes but are rather to methods of using DPD genes for detection of a mutation, human DPD genomic DNA is essential to practice the claimed invention. As such, and in view of the fact that said DNA was not known or conventional at the time the invention was made, it requires adequate written description.

As indicated by the Federal Circuit in *UC California v. Eli Lilly*, (43 USPQ2d 1398), a sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. The description of the functional characteristic of being a human DPD gene and the structural characteristic of comprising a sequence of nucleotides 432-435 of SEQ ID NO:1 and having either G or A at position 434 is insufficient to adequately describe the genus of human

DPD genes. The recited structural feature of the genus of recited human DPD genomic DNAs, i.e., comprising a sequence of nucleotides 432-435 of SEQ ID NO:1 and having either G or A at position 434, *does not* constitute a substantial portion of the genus as the remainder of the structure of human DPD genomic DNA is completely undefined and therefore encompasses widely variant species of DNAs. Also, in the event that other human dihydropyrimidine dehydrogenase genes exist, it is very unlikely that merely 4 nucleotides (432-435 of SEQ ID NO: 1) constitute a structural feature which is characteristic of some human dihydropyrimidine dehydrogenase genes but not others. Furthermore, the disclosure of a single species of human genomic DPD DNA, i.e., SEQ ID NO:1. does not provide adequate description in view of the fact that the prior art suggests variations within DPD genomic DNA and cDNA. Diasio et al. (WO 95/28489) teaches the presence of a polymorphism in DPD genomic DNA indicating the presence of at least two different alleles (page 97). Also, based on the prior art, it appears that the structure of a complete human genomic DPD DNA was not conventional at the time of the invention. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus. In regard to *In re Herschler*, it is noted that the structure and function of numerous steroids were well known at the time of the invention, which is not the case in the instant application.

15. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method for detecting a splicing defect in the human dihydropyrimidine dehydrogenase genomic DNA of SEQ ID NO:1 by determining the presence

of A or G at position 434 of SEQ ID NO:1, (2) a method for screening patients for sensitivity to 5-FU by isolating the human dihydropyrimidine dehydrogenase genomic DNA of SEQ ID NO:1 and determining the presence of A or G at position 434 of SEQ ID NO:1, or (3) the methods of (1) or (2) further comprising amplification of the nucleic acid of SEQ ID NO:1, does not reasonably provide enablement for (1) a method for detecting a splicing defect in *any* human dihydropyrimidine dehydrogenase gene by determining the presence of A or G at a position corresponding to nucleotide 434 of SEQ ID NO: 1 in any human dihydropyrimidine dehydrogenase genomic DNA comprising residues 432-435 of SEQ ID NO:1, (2) a method for screening patients for sensitivity to 5-FU by isolating any genomic DNA from the patient comprising positions 432-435 of SEQ ID NO: 1 and determining the presence of G at a position corresponding to position 434 of SEQ ID NO: 1, or (3) the methods of (1) or (2) further comprising amplification of *any* human dihydropyrimidine dehydrogenase genomic DNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claim 1 and 5 are drawn to a method of detecting a splicing defect in <u>any</u> human DPD gene by determining the presence of A or G at a position which corresponds to position 434 of

SEQ ID NO: 1 in any human dihydropyrimidine dehydrogenase genomic DNA comprising nucleotides 432-435 of SEQ ID NO:1. Claims 2-4 are directed to the method of claim 1 wherein any human dihydropyrimidine dehydrogenase genomic DNA is amplified. Claim 6 is drawn to a method of screening human patients for 5-FU sensitivity by (1) isolating any genomic DNA from the patient wherein said DNA comprises nucleotides 432-435 of SEQ ID NO:1 and (2) determining the presence of A or G at a position which corresponds to position 434 of SEQ ID NO:1. Claims 7-8 are directed to the method of claim 6 wherein any human dihydropyrimidine dehydrogenase genomic DNA is amplified.

The scope of the claims as described above is not commensurate with the enablement provided with regard to the extremely large number of human dihydropyrimidine dehydrogenase genes comprising nucleotides 432-435 of SEQ ID NO:1 (claims 1-5 and 7-9) and genomic DNA comprising nucleotides 432-435 of SEQ ID NO:1 (claim 6) broadly encompassed by the claims. While the specification is enabling for practicing the claimed methods with the human dihydropyrimidine dehydrogenase genomic DNA of SEQ ID NO:1, the specification is not enabling for the full scope of the claimed invention since it fails to disclose (1) the structure of other human dihydropyrimidine dehydrogenase genes or (2) other human genomic DNA comprising nucleotides 432-435 of SEQ ID NO: 1 (CGT), as encompassed by the claims wherein the presence of an A or G, as recited in the claims, is indicative of 5-FU sensitivity. Since the claims require a human genomic DNA comprising only 3 nucleotides (CGT) of SEQ ID NO: 1, it is very likely that other human genomic DNA may comprise these 3 nucleotides, therefore, it is unclear as to how one can reasonably expect that the presence of an A or a G in any genomic DNA comprising CGT is indicative of 5-FU sensitivity.

The argument can be made that other human dihydropyrimidine dehydrogenase genes required to practice the claimed method can be isolated by sequence homology with the structures disclosed in the instant application and the prior art. However, the state of the art teaches that functional annotation based on sequence homology is highly unpredictable and small structural changes can lead to major changes in function. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the structure of other human dihydropyrimidine dehydrogenase genes, the unpredictability of practicing the claimed method with other human genomic DNA comprising nucleotides 432-435 of SEQ ID NO: 1 as encompassed by the claims, and the unpredictability of the prior art in regard to isolating genes of similar function based on structural homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order

to screen and isolate those genes and genomic DNA as recited in the claims to practice the claimed method. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Conclusion

16. No claim is in condition for allowance.

17. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

18. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
June 12, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600